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Application of beta-blockers in burn management

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ABSTRACT

Severe burn injuries cause chronic inflammation, which produces a subsequent hypermetabolic response that starts immediately and persists for at least 3 years. The hypermetabolic state, which is thought to be due to postburn elevations of endogenous catecholamines and cortisol, is associated with a number of harmful physiologic derangements including immunosuppression, impaired wound healing, muscle catabolism, and hepatic dysfunction. Beta-blockers have become first line agents for reducing these adverse effects of hypermetabolism in severe burns. This review discusses the underlying pharmacological mechanisms demonstrated by clinical studies evaluating the safety and efficacy of beta-blockers in the management of burn injuries. A literature search was performed using the PubMed database to identify articles on beta-blockers and burn management. The review yielded 33 relevant results consisting of randomized controlled trials, original research articles, and meta-analyses in pediatric and adult burn patients. Propranolol administration reduced insulin resistance, lipolysis, proteolysis, cardiac work, and bone loss resulting from burn-associated hypermetabolism. Propranolol also effectively reduced myocardial stress, resting energy expenditure, and central deposition of fat. Recent studies have begun to evaluate incorporation of anabolic agents and rehabilitative exercise therapy. However, at this time propranolol continues to be the most effective therapy for reducing the hypermetabolic response and other morbidities resulting from burn injuries.

KEYWORDS Adrenergic; beta-blockers; burns; metabolism; treatment

CME

Target audience: All physicians

Learning objectives: After completing the article, the learner should be able to describe

1. The importance of hypermetabolism in the pathogenesis of burn injuries
2. The benefits of beta-blockers in burn injuries for preventing long-term complications
3. The effects of beta-blockers for pediatric burn patients for improving growth and metabolism after burn injuries

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Severe burn injuries trigger a catecholamine-mediated hypermetabolic response that impairs recovery if left untreated.[1] Patients with major burn injuries develop a number of harmful physiologic derangements including immunosuppression, impaired wound healing, cardiac stress, and hepatic dysfunction as a result of this elevated resting metabolic rate and protein and lipid catabolism. The resultant increase in catabolic processes reduces structural and functional fat and protein stores due to induction of sustained gluconeogenesis.[2,3] Without aggressive therapy, the dysregulation in energy expenditure and increased systemic inflammation deplete energy reserves and contribute to increased morbidity and mortality in burn patients.[3] In this review, we discuss clinical insights that have expanded our understanding of the pathophysiology of severe burns, specifically addressing the pharmacological mechanisms underlying hypermetabolism and the safety and efficacy of beta-blockers in the management of burn injuries.

BURN INJURIES AND HYPERMETABOLISM

Burn injuries still occur frequently, with a worldwide incidence of 0.14 to 12.3 per 100,000 population.[4] Severe burn injuries that cover >35% of the total body surface area (TBSA) produce chronic inflammatory and hypermetabolic responses that increase morbidity and mortality.[5,6] In otherwise healthy young adults, the energy expenditure can be as high as 5000 kcal in a 24-hour period. This leads to an increase in lipolysis, proteolysis, and gluconeogenesis resulting from elevated glucagon and insulin secretion.[7–9] Additionally, the release of cytokines and proinflammatory molecules leads to severe impairments in cardiovascular, respiratory, metabolic, and immunological function secondary to the hypermetabolic-induced changes.[7] The elevations in catecholamines and cytokines cause damage in adipose tissue and the dermis of the skin through activation of systemic macrophages, which in turn produce cytokines, eicosanoids, kinins, and histamines. The sustained elevations in catecholamines, corticosteroids, thyroid hormone, and growth hormones associated with the hypermetabolic response also produce hormonal abnormalities, increased liver and cardiac stress, impaired muscle function, and increased risk of sepsis, all of which increase morbidity and mortality for several months after the initial burn injury.[7–9]

Several studies have evaluated interventions to counteract the adverse effects of hypermetabolism with regard to burn management and treatment. The current therapeutic approach evolved from clinical observations demonstrating that the increase in basal metabolic rate in burn patients results from catecholamine stimulation of beta-adrenergic receptors due to an elevated neuroendocrine response.[1,10] The therapeutic use of beta-blockers to reduce the hypermetabolic response was subsequently championed by David Herndon and the burn team at the Shriners Burn Institute in Galveston, Texas. Several clinical trials have subsequently demonstrated that beta-adrenergic receptor blockade using propranolol is an effective intervention for reducing postburn catabolism and improving outcomes in severely burned patients.

METHODS

A literature search was performed using the PubMed database to identify articles on beta-blockers and burn management. The key words for the search were (burns) AND (hypermetabolism) AND (beta-blocker). A total of 44 studies from 1974 to 2020 were returned, from which 33 relevant results were selected, including randomized control trials (RCTs) and original research articles focusing on advances in beta-blockers in the prevention of hypermetabolism.

EVOLUTION OF BURN MANAGEMENT USING BETA-BLOCKERS

One of the initial observations by Szabó et al[10] evaluated the nonselective beta-blocker oxprenolol (Trasicor) in patients with approximately 20% TBSA burns. The study found that patients treated with oxprenolol lost less weight than the untreated control group (5.4%, n = 8 vs 9.2%, n = 15; respectively).[10] Another study by Breitenstein et al[11] compared the effect of intravenous vs oral beta-blocker administration on resting metabolic rate. In 10 patients with an average burn of 28% TBSA, the decrease in metabolism relative to the baseline resting metabolic rate produced by intravenous (1.55 kcal/min vs 1.44 kcal/min) and oral (1.45 kcal/min vs 1.36 kcal/min) administration of propranolol was similar. The resting energy expenditure was calculated from VO_2, VCO_2, and the energy equivalent of VO_2, corrected for the nonprotein respiratory quotient. The comparable decreases in lipid oxidation indicate that the route of administration does not affect the efficacy of propranolol-mediated reductions in hypermetabolism (i.e., lipid oxidation) in burn patients.

Given the efficacy of propranolol in reducing hypermetabolism, Herndon et al[12] wanted to determine if the

cardiovascular effects of catecholamines could be blocked in severely burned patients without adversely affecting protein or fat metabolism. The study included 16 patients with burns affecting >40% TBSA who were given either propranolol (nonselective beta-1 and beta-2 adrenergic receptor blocker) or metoprolol (cardiovascular-selective beta-1 receptor blocker) for 5 days. They found that while both propranolol and metoprolol produced equivalent reductions in heart rate, the selective beta-1 adrenergic receptor antagonist, metoprolol, did not prevent lipolysis, indicating that the increased lipolysis characteristically seen in severely burned patients is mediated by beta-2 adrenergic receptors. In contrast, propranolol effectively reduced lipid oxidation through a reduction in glycerol synthesis. Therefore, it is advantageous to use the nonselective beta-blocker propranolol to reduce hypermetabolism following a burn injury, with the added therapeutic advantage that propranolol also safely reduces cardiac work in adults.

Although previous studies had established the safety and efficacy of short-duration beta-blocker administration in severely burned adult patients, Baron et al[13] sought to determine whether propranolol could be safely given to pediatric burn patients for longer durations. Children aged 1 to 10 years (n = 22) with burns >40% TBSA were prospectively administered 0.5 to 1.0 mg/kg propranolol orally or intravenously every 8 hours for 10 days. Propranolol reduced heart rate between 10% and 13%, with no change in mean arterial blood pressure, plasma urea nitrogen, creatinine, or glucose levels. Moreover, no significant adverse events (e.g., hypotension, hypothermia, arrhythmia, or hyperglycemia) were noted. A subsequent RCT followed pediatric burn patients for 28 days.[14] Children with burns covering approximately 40% TBSA were randomized to groups that received oral propranolol titrated to reduce heart rate by 20% (n = 12) or placebo (n = 10). Over the course of treatment, fat-free mass was preserved in the propranolol group, whereas the control patients lost 9% of their fat-free mass. Similarly, a study by Wurzer et al[15] analyzed hemodynamic parameters in 121 pediatric burn patients followed for 28 days postinjury. Patients were randomized to groups receiving either 4 mg/kg/day propranolol (n = 59) or placebo (n = 62). The results indicated that propranolol reduces cardiogenic stress in pediatric burn patients without adversely affecting peripheral perfusion, wound healing, organ dysfunction, or mortality.

Building upon the preceding observations was a RCT that examined the outcomes (i.e., cardiac function, resting energy expenditure, and body composition) of long-term propranolol treatment in the pediatric patient population.[3] The study included 179 pediatric patients randomized to either the placebo (n = 89) or 4 mg/kg/day propranolol (n = 90) groups with follow-up for 12 months after sustaining a burn injury covering >30% TBSA. After 1 year, children treated with propranolol maintained a lower percentage of predicted heart rate compared to controls (110% vs 119%, respectively). The propranolol-mediated decrease in resting energy expenditure also resulted in a larger increase in peripheral lean mass at 1 year (28.3% vs 2.2% in the control group). The most common adverse events in both the placebo and propranolol groups were hypotension, bradycardia, hypoglycemia, cardiac arrhythmia, respiratory arrest, and sepsis-related deaths; however, these adverse events were rare.[3] Overall, the study showed that chronic propranolol treatment is safe and markedly decreases heart rate and cardiac work in pediatric burn patients. Additionally, propranolol treatment reduces hypermetabolism and reverses muscle-protein catabolism experienced by pediatric burn patients.[14] Furthermore, chronic propranolol treatment also increases lean body mass and bone mineral density, which may improve long-term growth and cardiac health. The finding that propranolol is safe when administered to pediatric burn patients for periods of 1 to 2 years for the purpose of reducing the hypermetabolic response was recently confirmed by Ojeda et al.[16] Thus, propranolol is equally safe and effective as a treatment for reducing hypermetabolism in both children and adults. However, cumulatively these studies suggest that the greatest benefit derived from beta-blockade pertains to sustained reduction of hypermetabolism in pediatric burn patients.

Despite several RCTs having demonstrated that propranolol reduces hypermetabolism and cardiac stress in burn patients, the optimal dosing and frequency to maintain the effects of propranolol in patients with severe burns was unknown. To address this limitation, Guillory et al[17] examined propranolol concentrations in 26 adult patients with burns covering approximately 30% of TBSA. The study divided patients between the placebo group (n = 10) and three dosing strategies: four times a day (Q6, n = 4), three times a day (Q8, n = 6), and one time a day (Q24, n = 6). Although all three dosing strategies achieved reductions in heart rate, administration of propranolol using the Q6 dosing strategy was more effective at reducing heart rate than the Q8 dosing strategy. In contrast, the Q24 dosing strategy using an extended-release formulation of propranolol was equally effective at reducing heart rate and cardiac myocardial oxygen consumption relative to dosing at Q6 intervals. Accordingly, either Q6 or Q24 extended-release propranolol dosing is an effective approach to attenuating hypermetabolism and cardiac work in adult burn patients.

An RCT by Williams et al[18] sought to address the optimal dose of propranolol for reducing hypermetabolism in pediatric burn patients. The study included 406 children with burns covering >30% of TBSA randomized to receive either standard care (controls, n = 235) or standard care and propranolol (n = 171). Children required 4 to 6 mg/kg/day of propranolol orally to maintain an average decrease of 15% in heart rate relative to control patients, with similar reductions in male and female children. Furthermore, the decrease in heart rate was comparable in patients with burns covering 30% to 60% TBSA, 60% to 80% TBSA, or >80% TBSA. The observed increase in cardiac output was significantly reduced in children treated with propranolol at 2 weeks postinjury relative to the untreated controls (135% vs 158%, respectively). Overall, administering 4 mg/kg/day of

propranolol effectively prevented the hypermetabolic state in pediatric burn patients.

COMBINATION THERAPIES

In recent years, there has been growing interest in improving lean body mass and bone mineral content through the concurrent administration of propranolol and anabolic agents. However, the initial observation by Hart et al[16] demonstrated that growth hormone together with propranolol did not stimulate additional muscle mass when administered to burn patients. Subsequent studies have evaluated testosterone agonists, such as oxandrolone,[19] which binds directly to intracellular androgen receptors in skeletal muscle, leading to increased muscle protein synthesis.[20–22] Oxandrolone also competitively inhibits glucocorticoid receptors, which reduces cortisol-mediated muscle catabolism; both processes are believed to result from an increase in insulin-like growth factor-1 and may translate to increased weight gain, preservation of lean body mass, improved bone mineral density, and reductions in the length of hospital stay.[20–22] Accordingly, Herndon et al[19] investigated whether propranolol and oxandrolone act synergistically to attenuate growth arrest and improve the rate of growth in pediatric patients. The study included 612 patients with an average burn covering 52% TBSA randomized to receive placebo (n = 248), propranolol (n = 194), oxandrolone (n = 67), or propranolol plus oxandrolone (n = 103) for 1 year. Both propranolol and oxandrolone reduced hypermetabolism in burn patients, resulting in increased bone mineral content, lean body mass, and protein synthesis. However, combined use of oxandrolone and propranolol reduced the period of growth arrest by 84 days and increased the growth rate by 1.7 cm/year compared to the control group. A prior study by Guillory et al[23] showed that oxandrolone coadministration does not affect plasma propranolol concentration in severely burned patients. Therefore, combining oxandrolone and propranolol offers a potential advance for reducing burn-induced growth arrest in pediatric patients.[19]

The synergistic action of oxandrolone and propranolol encouraged further investigation of whether rehabilitative exercise training (RET) might further improve cardiorespiratory outcomes (e.g., hypermetabolism, body composition, and muscle function). RET uses chronic resistive and aerobic exercise to improve skeletal muscle strength, increase lean body mass, and improve joint range of motion.[24] Specifically, the RET training program includes both resistive and aerobic components with varying levels of frequency, intensity, duration, and mode of exercise. Therefore, Chao et al[24] studied the hypothesis that RET combined with oxandrolone and propranolol would improve muscle function and protein turnover among severely burned children. The study enrolled 42 pediatric patients with burns covering approximately 30% TBSA who received either RET and a placebo (n = 22) or RET plus oxandrolone and propranolol (n = 20) within 96 hours of admission. They found that early outpatient exercise rehabilitation programs improve body composition, muscular function, and cardiorespiratory fitness in pediatric burn patients who were administered propranolol and oxandrolone. Although combinations of RET and dual drug therapy were successfully applied to burn patients, it was uncertain whether combining exercise training with propranolol alone could increase VO_2 max in pediatric burn patients. The results thus far indicate that administration of propranolol may improve cardiorespiratory capacity in burn patients without rehabilitation[25]; however, further research is needed to evaluate whether the inclusion of rehabilitation services can improve overall cardiorespiratory capacity.

Several RCTs have established that propranolol effectively reduces postburn complications by decreasing hypermetabolism and cardiorespiratory stress.[26,27] A meta-analysis by Chew et al[27] showed that propranolol reduced cardiac work, rate pressure product, resting energy expenditure, body mass, and bone mineral loss in five RCTs. The propranolol was also well tolerated with no difference in adverse events among burn patients. However, propranolol did not reduce length of stay for hospitalized patients or mortality.[27] This outcome was confirmed in a second meta-analysis by Manzano-Nunez et al,[26] who found that propranolol did not reduce mortality, sepsis, or length of hospital stay. Conversely, a recent study by Jeschke et al[28] showed that propranolol does not increase inflammation, sepsis, or risk of infection in pediatric burn patients. Although propranolol does not reduce burn mortality, other pharmacological agents, such as oxandrolone, may act synergistically with propranolol to reduce mortality and sepsis. Therefore, future RCTs may examine whether combinations of pharmaceutical agents and rehabilitation strategies may improve overall quality of life for burn patients.

CONCLUSION

The beta-blocker propranolol continues to be the first-line drug administered for the management of hypermetabolism in patients with severe burns.[26,27] The catecholamine-induced increase in metabolism increases insulin resistance, lipolysis, cardiac work, bone loss, and proteolysis, which further exacerbates the hypermetabolic state associated with burns. Without treatment, hypermetabolism can lead to increased morbidity and mortality among burn patients. Currently, propranolol is used to reduce thermogenesis, tachycardia, and resting energy expenditures following burn injuries.[9,14,29] Propranolol also reduces peripheral lipolysis, fatty infiltration in the liver, and skeletal muscle wasting through blockade of the beta-2 adrenergic receptor.[9,14,30,31] Recent clinical studies also suggest that propranolol may prevent postburn insulin resistance.[18] Specifically, administration of propranolol decreased the amount of insulin required to attenuate elevated glucose levels after burn injury through improved hepatic phosphatidylinositol 3-kinase/Akt signaling.[18,32] Propranolol remains an effective therapy for reducing the hypermetabolic response and comorbidities from burn injuries. However, there is insufficient data to show propranolol reduces burn-associated mortality or length of

hospitalization. Future clinical trials with larger sample sizes and long-term follow-up are needed to determine whether beta-blockers reduce mortality and treatment costs for burn injuries. These studies would also benefit from stratifying pediatric and adult patients to determine whether the efficacy of beta-blockers differs in either population. Furthermore, additional research is required to assess whether combining other pharmaceuticals, like anabolic agents, with propranolol may further reduce hypermetabolism and other postburn complications.

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